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Laser Fabrication of Polymeric Microneedles for Transdermal Drug Delivery

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Abstract

Microneedles provide a transdermal pathway for drug delivery, cosmetic infusion, vaccine administration, and disease diagnostics. Microneedle fabrication relies on the interplay of several variables which include design parameters, material properties, and processing conditions. In this research, our group explores the effect of design parameters and process variables for laser ablation of microneedles within a Polymethyl methacrylate (PMMA) mold. An Ytterbium laser (200W) was utilized to study the effect of five inputs factors (laser power, pulse width, number of repetitions, laser waveform, and interval time between laser pulses) on two output factors (diameter and height) of the fabricated microneedles. Polydimethylsiloxane (PDMS) polymer was cast within the PMMA microneedle mold. Scanning electron microscopy (SEM) was employed to image topographical features of the microneedles. Further, mechanical testing of the microneedles was conducted to evaluate the buckling load and deformation behavior of the microneedle array. A 20W pulse laser with trapezoidal waveform resulted in optimal microneedle topography with an aspect ratio of 1.2. ANOVA results ($\alpha = 0.05$) depicted that laser power and number of repetitions were significant factors determining the geometrical features of the microneedle array. This research establishes a framework for the design and manufacturing of customized microneedles for precision medicine.

Keywords
Microneedle, transdermal, drug delivery, laser ablation, Ytterbium laser.

1. Introduction
Microneedles provide promising pathway for transdermal drug delivery and have attracted attention by several researchers. A number of studies have demonstrated the potential of microneedle in different fields. These include their application in drug delivery [1][2], cosmetics [3][4][5], vaccine delivery [6][7], and disease diagnostics [8][9]. The microneedle approach has several advantages over other intravenous drug delivery methods which minimizes the passage of high potency drugs through the human organs such as the liver [10]. Also, using a microneedle offers a pain-free drug delivery treatment experience [11].

Laser ablation is a microfabrication technique that can be used to manufacture microneedles. Chung and Tu fabricated a microneedle array by using CO_2 laser [12]. Another study used an excimer laser to manufacture a microneedle array [13]. Moreover, Zheng et al. chose a femtosecond laser ablation method [14]. This paper proposes an ytterbium laser to manufacturing microneedle molds (array) for transdermal drug delivery application. The ytterbium laser offers advantages over other types of lasers [15]. It is known to have high melting efficiency [16], high productivity and lower energy consumption compared to CO_2 lasers [17].

Microneedle fabrication depends on several variables and is underexplored in literature. Chung and Tu applied different laser power and scanning speed values to study their effect on the fabricated needles [18]. Another research studied the influences of pulse shot number and hole diameter on fabrication depth, hole diameter, and sidewall smoothness [19]. To explore the comprehensive relationship this research paper investigates the effect of five different process parameters on the microneedle fabrication. These parameters include laser power, pulse width, pulse repetition, pulse interval, and design profile (waveform).

2. Material and Methodology

2.1. Material

In this study, the microneedle arrays were produced using a Polymethyl methacrylate (PMMA) material as a substrate. Polydimethylsiloxane (PDMS) was used to cast the mold in order to capture the inner shape of the microneedle array.

2.2. Experiment Procedures

The proposed procedure for this experiment was followed as shown in **Figure 1**. The manufacturing methods start with setting a desire values for laser power, pulse width, waveform, interval time and number of pulses. A commercial laser system (TLR-1070, IPG photonics) used to create a hole on the PMMA substrate. Then, poured a mix of part 1 and 2 of PDMS (Dow SYLGARD™ 184 Silicone Encapsulant Clear) material to have an inverse mold of the inner shape of the substrate. Finally, capturing the topology of the needles by using a scanning electron microscope (SEM). These procedures were repeated to produce different microneedles using different parameter values each time.

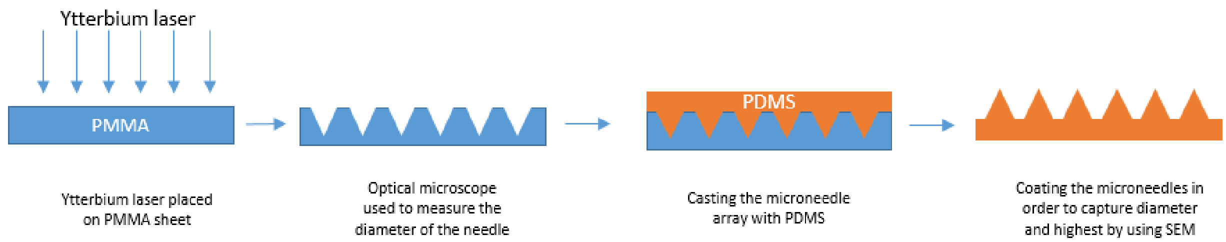

Figure 1: Microneedle fabrication using ytterbium laser

2.3. Pilot Study

Due to variety of parameter values, the study proposed a pilot study to narrow down the range of data to best variable's value to be conducted for further study. The pilot study concluded the optimal values for the parameters after more than 200 runs experimental runs as follows:

- Laser Waveform: the best outcome of the microneedle was the trapezoid and square waveform. This exclude the triangle shape from further study where it required a high power to performed which results a large diameter the software options are: Square, Triangle, and Trapezoid shape.
- Laser Power: The laser power should be ranged between 30 to 40 watts in order to get the perfect outcome. Less than 30 watts will have no effects on the substrate and more than 40 will results having a large needle.
- Pulse Width: the best pulse width range varies from 3 to 5ms to approach the desired outcome. Higher/lower values from 3 to 5ms of pulse width will result undesired outcomes.
- Number of repetitions: the study proposed 50 and 100 number of repetitions to be considered for further study due to optimal results of using these values.
- Interval time: the optimal interval values were from 0 to 50ms based on trial experiments.

2.4. Design of Experiment

Conducting a full design of experiment assured better understanding of the parameter effects and their relationship to the outcome of the study. The study proposed a design of five independent variables, with two levels and three replicates (**Table 1**). These factors are the waveform (square and trapezoid), power (30 and 40 watts), pulse width (3 and 5), repetition (50 and 100), and interval (0 and 50ms). The outcomes of the study where the diameter and depth of the microneedle captured using SEM. For that, 96 runs were conducted to conclude this study.

Table 1: Design of Experiment

Factor	Level		Outcomes	
	1	2		
Waveform	Square	Trapezoid	Diameter	Height
Power (watt)	30	40		
Pulse width (ms)	3	5		
Repetition	50	100		
Interval (ms)	0	50		

2.5. Mechanical testing

An axial force test was performed using (Instron® Model 5542) to study the relation between displacement and the force. The station applied force parallel to the microneedle on (-y-axis) (**Figure 2**). The needle was placed on the bottom fixture of the station. A bottom of each single needle was gluing on circle glass to make sure not slipping during the test and to create a constant experiment. The outcome of this test was to capture the force, displacement, stress, and strain of the microneedle.

Figure 2: Mechanical deformation testing set-up

3. Result and Discussion

The results of all 96 runs were well-designed microneedles array except one microneedle (trapezoid shape, 30watt power, 3mm pulse width, 50 repetitions, and 50mm interval time). The results of microneedle diameters ranged from 0.2mm – 1.6mm and height range from 0.4 to 1.7mm. **Figure 3a** and **3b** shows an SEM images of example produced microneedle. This concluded that all chosen parameters set were fully sufficient for microneedles design.

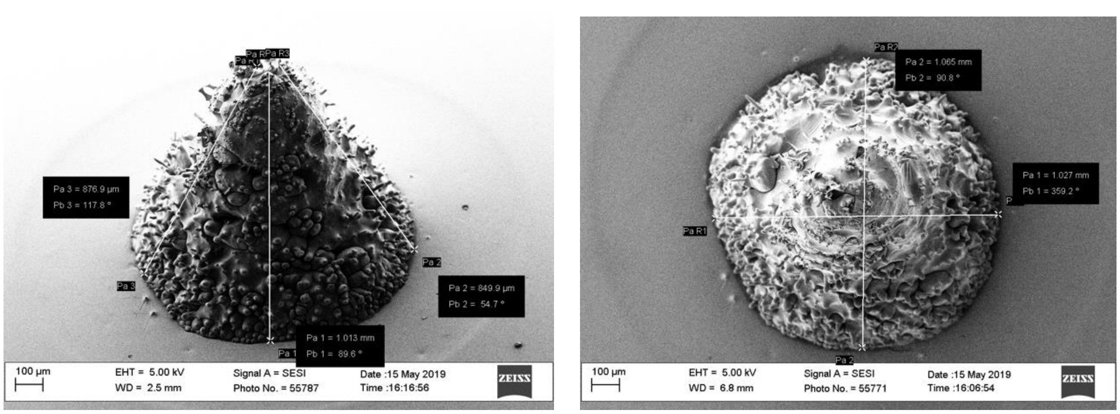

Figure 3: SEM image of a microneedle **(a)** side view **(b)** top view

3.1 Effect of parameters on diameter and height of the needles

The results of the microneedle's diameter and height were evaluated and test it in Minitab and SAS software. **Figures 4a** and **4b** shows that all factors are statistically significant at the 0.05 level with the current design model. The following is the rank of parameters effecting the diameter starting with the high impact (interval, pulse width, waveform, laser power, and repetition, respectively). On the other hands, the interval parameter has the highest impact factor on the height of the needle followed by laser power and pulse width. The waveform and repetition place at last in the value of effecting the heights. Also, some interactions between factors shown a significant impact on the output of the experiment. 14 interactions between factors are considered a significant impact on the diameter of the microneedle design. Also, 7 interactions have an impact of the height of the microneedles. Here a summarized of each single factor:

- Waveform: the waveform parameter is affecting both diameter and height of the needles. The square waveform has a higher impact on the needle's diameter and height when compare it to the trapezoid shape. The trapezoid waveform associated with a lower mean for both diameter and height of the needles.
- Laser power: increasing in laser power values will results in increasing the diameter and height of the needles (direct correlation). However, the laser power has the highest impact on needle's height compared to the diameter.
- Pulse width: high values set of pulse width will results in larger diameter and taller height of the needle (direct correlation). However, the pulse width facto affecting the height slightly higher than the diameter.
- Repetition: increase the number of laser pulse exposed to the PMMA substrate will result in larger diameters. Comparing to other factors, this factor is the lowest factor that affecting the experiment's outputs
- Pulse interval: the interval time between the laser and other is has the highest impacts on the diameter and height. The interval factor has an inverse relationship to the diameter and height of the needle.

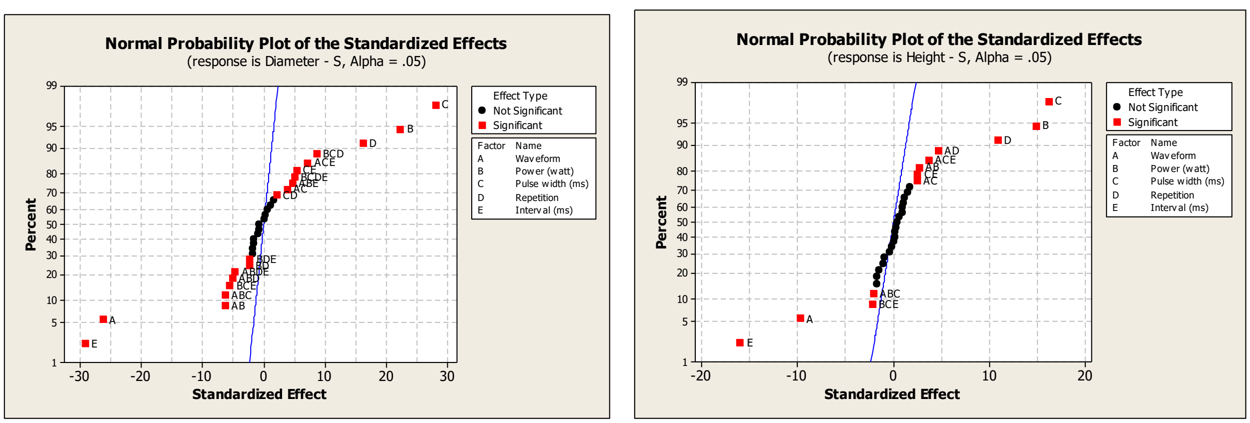

Figure 4: Normal probability plot of the standardized effects response is **(a)** Diameter **(b)** Height

3.2 Mechanical Testing

The mechanical force failure test conducted to all 96 microneedles fabricated earlier. The maximum force value ranged between -0.225 and -13.031N. **Figure 5** shows the main effects plot between the parameters and the average displacement when the force = -0.2N. the square waveform parameter associated with the highest mean displacement. However, the waveform has no effects on the displacement value and is not significant. The laser power, pulse width, number of repetitions, and interval time with 40, 5, 100, 0 respectively has the highest mean displacement values in this experiment and these parameters are statistically significant. **Figure 6** shows a load displacement curve for a different microneedle sets as followed:

- MN1 (Waveform: Square, Power: 40watt, Pulse Width: 3ms, repetition: 100, and interval: 0)
- MN2 (Waveform: Square, Power: 40watt, Pulse Width: 3ms, repetition: 100, and interval: 50)
- MN3 (Waveform: Trapezoid, Power: 30watt, Pulse Width: 5ms, repetition:50, and interval: 0)
- MN4 (Waveform: Trapezoid, Power: 40watt, Pulse Width: 3ms, repetition: 100, and interval: 50)

The elastic deformation of MN1 shows that constant displacement movement along with force values, however, the failure force was -0.54N with a displacement value of -0.2mm. The plastic deformation remains till the force and displacement values reaches the value of -0.77N and -1.2mm. MN2 shows that the needles failure point at force = -

0.56N with displacement value of -1.26mm. The MN3 start to show a displacement at force of -0.32N and continue to absorb the force till reach the value of -0.7N. Finally, a significant displacement of MN4 when the force value reach -0.55N.

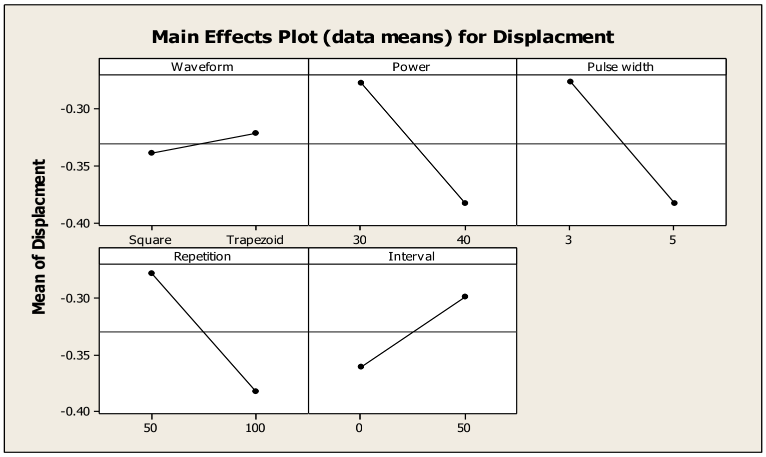

Figure 5: Main effects plot (data means) for displacement.

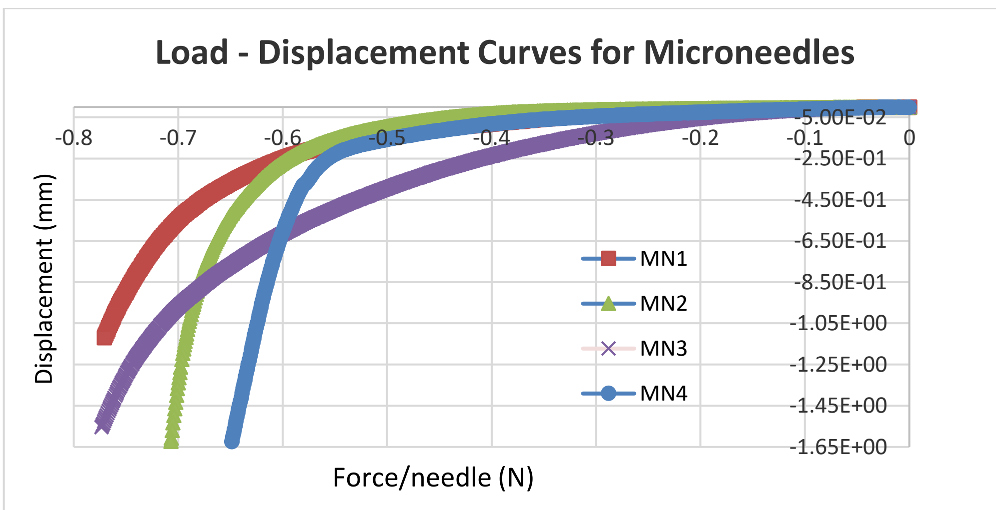

Figure 6: Load-displacement curve for five different microneedles

4. Conclusion

The microneedle concept has been evolved over the years and used for different application such as drug delivery, cosmetic application, vaccine delivery, and disease diagnosis. The research sought a new approach in fabrication a microneedle using an ytterbium laser. This research introduced different parameters (waveform, laser power, pulse width, repetitions, and interval time) sets to fabricated a desire diameter and height of a microneedle. Due to the large combination of parameter sets, a pilot study conducted to optimize reasonable range of each parameter. A PMMA substrate was used to create the needle holes by using the laser pulses. A PDMS polymer was casted on PMMA microneedle mold. A SEM was employed to capture the topographical feature of the microneedle. Also, a mechanical deformation behavior was studied on the microneedle using a mechanical testing. This research provides a framework for designing and manufacturing a customized microneedle and contributes to the next generation of microneedle array manufacturing. Moreover, the study proposed a predictive model for fabricating a customized microneedle array.

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